DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

May 5, 2011

Ms. Denlyn K. Atherton
Sr. Patent Administrator
Harvard University Office of Technology Development
1350 Massachusetts Ave. #727
Cambridge, MA 02138

Re: Request for Waiver of the Preference for United States Industry

EIR: 3212901-06-0093
EIR TITLE: STOCHASTIC OPTICAL RECONSTRUCTION MICROSCOPY PROVIDES SUB-DIFFRACTION-LIMIT IMAGE RESOLUTION
EIR: 3212901-07-0113
EIR TITLE: SUB-DIFFRACTION LIMIT IMAGE RESOLUTION IN THREE DIMENSIONS (Also Patent Title)

Patents and	11/605,842	Filing Date 11/29/2006	3212901-06-0093
Patent applications:	7,776,613	Issue Date 8/17/2010	3212901-06-0093
	12/012,524	Filing Date 2/1/2008	3212901-06-0093
	12/795,423	Filing Date 6/7/2010	3212901-06-0093
	12/746,784	Filing Date 6/8/2010	3212901-07-0113

NIH Funding Agreement: GM068518
Inventors' Names: Xiaowei Zhuang, Bo Huang, Wenqin Wang, Wilfred M. Bates

Dear Ms. Atherton:

This letter is in response to the US Manufacturing Waiver Request submitted by Harvard University on the above-referenced invention conceived or first actually reduced to practice through an NIH funding agreement.

Below is a summary of the scientific, commercialization and licensing reviews of the Subject Invention that is the subject of this Manufacturing Waiver; this Office concurs with those reviews and further agrees that it is in accord with the terms and conditions of the funding agreements under which it was made.

Commercialization Background and Analysis

This technology concerns sub-diffraction image resolution and other imaging techniques, encompassing resolution in three dimensions. Specifically, improved methods of imaging using fluorescence microscopy to provide enhanced resolution and permit the creation of images of bio-molecular cells and complexes as small as twenty nanometers. This is a ten-fold improvement in resolution over existing technologies.

Harvard states that approximately 95 percent of the current market in fluourescence microscopes is split among four companies, including its licensee, Nikon (Japan). However, these companies are neither U.S.-based nor do they have the capability to manufacture the technology within the U.S. Harvard explains that the addition of the technology into microscopes involves the incorporation of parts and software during the complex manufacturing process of a normal fluorescence microscopy unit. Production requires extensive quality control testing prior to integration; and similarly, research and development for the overall unit must occur in close proximity to manufacturing so that workers with the required expertise can participate in all stages. Given this, Harvard states that without a grant of the waiver of the Preference for United States Industry, Nikon would have to

establish new U.S. manufacturing facilities for the overall product into which the technology is integrated – however the microscope units would not represent a substantial source of profit to merit such an investment.

Harvard further provides that it made reasonable efforts to license the invention domestically, [redacted] (b)(4)

Summary

Based on the information you have provided about the current circumstances for this technology, your request for a manufacturing waiver has been approved to use the licensees' currently existing facilities as discussed in the waiver request. Should these existing facilities become inadequate or insufficient, manufacturing capacity in the United States must be developed or another Waiver of the Preference for United States Industry must be requested. [redacted] (b)(4)

All other terms and conditions of the funding agreements, with the exception of the Preference for United States Industry as outlined in this letter, remain in effect.

Please feel free to contact us should you have any additional questions regarding this issue.

Sincerely,

John Salzman
Assistant Extramural Inventions Policy Officer
Division of Extramural Inventions and Technology Resources
Office of Policy for Extramural Research Administration, OER, OD

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Pages 3 through 4 redacted for the following reasons:
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August 10, 2011

Submitted via iEdison

Division of Extramural Inventions and Technology Resources, OPERA, OER
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Re: Power of Attorney – iEdison Request ID 2482 (NIH Grant No. GM068518)

To Whom It May Concern:

The President and Fellows of Harvard College ("Harvard") hereby authorize Jay P. Urwitz and Edwin O. Childs Jr., of Wilmer Cutler Pickering Hale and Dorr LLP ("WilmerHale"), to represent Harvard before the National Institutes of Health ("NIH") in connection with iEdison request ID 2482, in which Harvard requested a waiver of the U.S. manufacturing preference under the Bayh-Dole Act, 35 U.S.C. § 201 *et seq.*, for inventions created under NIH Grant No. GM068518. WilmerHale is permitted to do and perform any and all acts on Harvard's behalf which may be necessary or desirable to facilitate and complete iEdison request ID 2482.

This authorization is valid until revoked by Harvard in writing.

By signing below, I affirm that I am empowered to grant this authorization.

Respectfully submitted,

Anne Craig

Anne Craig
Director of Intellectual Property
Harvard University

cc: Jay P. Urwitz, WilmerHale

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October 20, 2010

Confidential Treatment Requested

TO: Division of Extramural Inventions and Technology Resources, OPERA, OER
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Space and Naval Warfare Systems Center Pacific
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FROM: Wilmer Cutler Pickering Hale and Dorr LLP
on behalf of Harvard University

RE: Request for Waiver of the Bayh-Dole Act's U.S. Manufacturing Preference, NIH Grant No. GM068518, SPAWAR Grant No. N66001-04-1-8903

Dear Sir or Madam:

Wilmer Cutler Pickering Hale and Dorr LLP, on behalf of The President and Fellows of Harvard College ("Harvard"), hereby submits this request for a waiver of the U.S. manufacturing preference under the Bayh-Dole Act, 35 U.S.C. § 201 *et seq.*, for the development and production of certain florescence microscopy equipment. Harvard has filed patents[1] for the intellectual property that is being licensed (the "Inventions"). It requests a waiver of the domestic manufacturing preference because domestic manufacturing of florescence microscopy imaging equipment based on the Inventions is not commercially feasible, and because reasonable

[1] Patent application number 11/605,842, "Sub-diffraction Image Resolution and Other Imaging Techniques," filed November 29, 2006 (priority date August 7, 2006), is set to issue on August 20, 2010. All other related patent applications are pending.

but unsuccessful efforts were made to grant licenses on similar terms to those who would be likely to substantially manufacture in the U.S.

The Inventions offer improved methods of imaging using florescence microscopy to provide enhanced resolution and permit the creation of images of bio-molecular cells and complexes as small as twenty nanometers. The device and techniques are called super-resolution fluorescence microscopy. The Inventions were developed by researchers at Harvard and Harvard has negotiated and seeks to grant an exclusive license to the Nikon Corporation ("Nikon"). The underlying intellectual property was developed under grants awarded by the National Institute of Health ("NIH") and the U.S. Navy's Space and Naval Warfare Systems Center Pacific ("SPAWAR").

This application contains confidential commercial and financial information and trade secrets. Public disclosure of this highly sensitive proprietary information could adversely affect both Harvard and Nikon. Therefore, Harvard and Nikon believe that this document and any other documents submitted in connection with this request are exempt from disclosure under the Freedom of Information Act, 5 U.S.C. § 552.

Wilmer Cutler Pickering Hale and Dorr LLP is submitting this request on behalf of the Office of Technology Development, Holyoke Center 727, 1350 Massachusetts Avenue, Cambridge, MA 02138.

I. Product Background

A. NIH Grant Support

Dr. Xiaowei Zhuang, Professor of Chemistry and Chemical Biology and Physics at Harvard University, and a Howard Hughes Medical Institute Investigator, has received grants

from NIH and SPAWAR to support her research on florescence microscopy. Identifying information for each grant is set forth below.

NIH Grant Number: GM068518

Grantee Institution: Harvard University

Project Title: Cellular Entry of Influenza by Single-Particle Imaging

SPAWAR Grant Number: N66001-04-1-8903

Grantee Institution: Harvard University

Project Title: Integrated Nanoscale Nanowire Correlated Electronic Nanosensing Technology (INNOCENT)

B. Intellectual Property Developed from the Research

These NIH and SPAWAR grants provided funding for developing the Inventions that Harvard seeks to license to Nikon. First, NIH and SPAWAR grant funding was used in the process of developing the Invention identified as "Sub-Diffraction Image Resolution and Other Imaging Techniques." This invention was disclosed under patent application numbers 11/605,842; 12/795,423; and 12/012,524.

Second, NIH funding was used in the process of developing the Invention identified as "Sub-Diffraction Limit Image Resolution in Three Dimensions." This invention was disclosed under patent application number 12/746,784.

C. Licensing Arrangements

Harvard, as the owner of the intellectual property described above, has negotiated a licensing agreement with Nikon in order to promote the development and production of

advanced fluorescence microscopy equipment based on the Inventions (the "Agreement"). The Agreement provides Nikon (b)(4) (b)(4)

II. Importance of the Technologies

A. Fluorescence Microscopy

Florescence microscopy is widely used in molecular and cell biology and other biomedical applications for imaging at the cellular and sub-cellular level. It is an essential tool in biological research. The ultimate goal of fluorescence microscopy is to observe cellular and sub-cellular structures and live cellular processes, including the processes leading to disease states such as cancer, with a high spatial and temporal resolution. Fluorescence microscopy is the most suitable method for studying the dynamic behavior within cells monitored by real-time imaging of live cells. This stems from the ability of fluorescence microscopy to detect individual cellular components with a high degree of specificity amidst non-fluorescent material. The sensitivity of fluorescence microscopy is high enough to detect as few as 50 molecules per cubic micrometer. Different molecules can be labeled with different fluorophores, allowing multiple types of molecules to be tracked simultaneously. These factors combine to provide fluorescence

microscopy with a distinct advantage over other optical imaging techniques, for both *in vitro* and *in vivo* imaging applications.

Despite its advantages, standard fluorescence microscopy has not been useful for ultra-structural imaging, due to a resolution limit of about half the wavelength of the fluorescence set by the diffraction of light. Several approaches have been employed to try to pass this diffraction limit, including near-field scanning optical microscopy (NSOM), stimulated emission depletion (STED), reversible saturable optical linear fluorescence transition (RESOLFT), and saturated structured-illumination microscopy (SSIM), but each has certain unsatisfactory limitations. Electron microscopy is often used for high resolution imaging of biological samples, but such microscopy uses electrons rather than light, and is difficult to use with biological samples due to its preparation requirements. Accordingly, new techniques have been needed to harness the benefits of fluorescence microscopy for ultra-resolution imaging of biological and other samples, and to enable non-invasive imaging of live samples with molecular specificity. The ability to observe cellular processes at molecular resolution would further our understanding of cellular physiology, including processes that lead to disease.

B. The Inventions and Their Research Value

These inventions represent significant steps forward in the development of fluorescence microscopy. They will supplement existing fluorescence microscopy equipment and enhance the ability of existing equipment to view images at a resolution of approximately twenty nanometers, a ten-fold improvement over existing technologies. The first invention describes and claims the stochastic optical reconstruction microscopy ("STORM") method of imaging fluorophores with a resolution of twenty nanometers. It does this by using a new class of photoswitchable

fluorescent entities[2] to specifically label a particular target molecule in the sample. The STORM method uses a sufficiently low intensity flash of light from a laser, which excites only a small subset of the fluorophores at a time. The excited fluorophores are sufficiently far apart that their location can be found with a high degree of accuracy. By repeatedly flashing the sample with low intensity light, one can construct an image of the sample with a resolution of around twenty nanometers. One can also use different fluorescent entities fluorescing at different wavelengths to label different target molecules in the sample, providing multi-color STORM. The second invention is three-dimensional STORM, which provides for imaging in the z direction, as well as the x and y directions of regular STORM, resulting in a three-dimensional representation of the sample. The images that STORM produces are among the clearest and most detailed of any ever produced by fluorescence microscopy equipment. STORM will allow research at the sub-cellular level to progress rapidly. It will increase our knowledge of cellular structure and function which, in turn, will increase our ability to detect, treat, and prevent disease.

III. The Bayh-Dole Act's U.S. Manufacturing Preference

Because of the grant funding provided by NIH and SPAWAR, the Inventions being licensed to Nikon are "subject inventions" to which the requirements of the Bayh-Dole Act (the "Act") apply. However, the substantial manufacturing provisions of the Act may be waived by the agency under whose funding agreement the invention was created. 35 U.S.C. § 204. For such a waiver to occur, one of two circumstances must be demonstrated. First, domestic manufacturing must not be "commercially feasible" under the circumstances. *Id.* Alternatively, "reasonable but unsuccessful efforts" must have been made to "grant licenses on similar terms to

[2] The photoswitchable dyes themselves are not being licensed to Nikon.

potential licensees that would be likely to manufacture the invention substantially in the United States." *Id.* The Inventions qualify for a waiver of the domestic manufacturing provisions under either standard, as will be demonstrated below.

IV. Domestic Manufacturing of the Inventions is not Commercially Feasible

A waiver of the domestic manufacturing preference should be granted because domestic manufacturing of the Inventions is not commercially feasible. Only four companies can fully implement the Inventions, because those companies have the otherwise technically sophisticated products which are necessary for the Inventions to be useful and the ability to manufacture in the necessary quantities. None of these companies is based in the United States and none has the capability to manufacture the Inventions in the United States. Because the Inventions would be implemented as small-cost additions to existing products, transferring overseas operations to the United States would not be feasible. Thus, in order for these Inventions to be commercialized, manufacturing must occur overseas.

A. Current Market Structure

Approximately ninety-five percent of the current market in fluorescence microscopes is split among four companies: Carl Zeiss AG and Leica Microsystems, which manufacture in Germany, and Olympus Corporation and Nikon, which manufacture in Japan. In total, roughly five hundred top-end fluorescence microscopy units are sold worldwide each year. On average, these fluorescence microscopy systems cost between $150,000 and $250,000 per unit. Adding the Inventions to a normal system would cost an additional (b)(4) The addition of the Inventions involves (b)(4)

(b)(4)

B. Barriers to Manufacturing in the United States

None of the four leading companies has facilities in place to manufacture these Inventions in the United States. Currently, all manufacturing of fluorescence microscopy equipment by these companies occurs in Japan or in Europe. Nikon's florescence microscopy-related manufacturing, research, and development facilities are all located in Japan.

The equipment is (b)(4) (b)(4) Therefore, manufacturing of one element of the system cannot be separated from manufacturing of the rest. The manufacturing process requires precise calibration by expert engineers. As part of this process, the equipment is subject to extensive quality control testing requiring prior integration of the Inventions. Similarly, research and development of the overall product must occur in close proximity to manufacturing so that workers with the necessary technical expertise can participate in all stages, as production of such complex equipment involves an iterative process of improving development methods. In order to incorporate these Inventions into fluorescence microscopy equipment within the United States, (b)(4)

Although the Inventions represent notable steps forward in fluorescence microscopy technology, (b)(4)

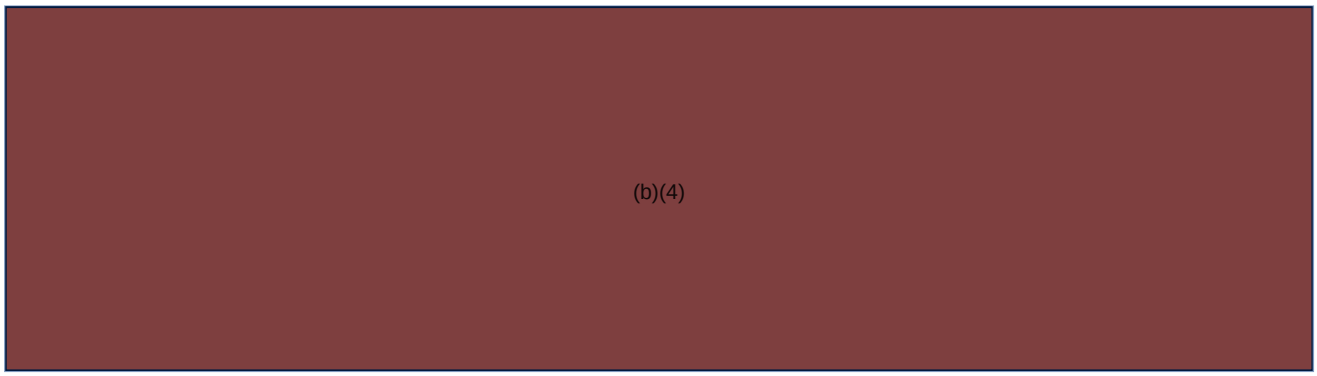
V. Harvard has Made Reasonable but Unsuccessful Efforts to License the Inventions Domestically on Terms Similar to the Terms Offered to Nikon

The domestic manufacturing requirement can also be waived where a grantee has made "reasonable but unsuccessful efforts . . . to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States." 35 U.S.C. § 204. Harvard has made extensive efforts to locate and identify a domestic manufacturer for the Inventions. (b)(4)

Approximately one year ago, (b)(4)

(b)(4)

(b)(4)



VI. Waiving the Domestic Manufacturing Preference is in the Best Interests of the United States

Because of the difficulties described above, commercial development of the Inventions is only practical overseas. Given the importance of florescence microscopy equipment to fundamental research and the risks of delaying future insights into significant threats to public health, it is therefore in the best interests of the United States to waive the domestic manufacturing preference and allow Nikon to develop the Inventions in Japan.

Even if the Inventions are developed overseas, other economic benefits will accrue to the United States. (b)(4) (b)(4) which will keep the United States at the forefront of research and development in this area, and it may assist the further development of fluorescence microscopy-related research in the United States. In addition, Nikon has several large domestic locations that handle other corporate functions, including import-related activities, sales for the United States and Latin America, and maintenance services. The products manufactured in Japan that include the Inventions will be imported, sold, and serviced by these domestic branches of the licensee.

VII. Conclusion

Harvard requests that the domestic manufacturing preference be waived and that overseas manufacturing of the Inventions be permitted. Domestic producers of fluorescence microscopy products lack the infrastructure within the United States needed to manufacture these products. Given the limited size of the worldwide market for fluorescence microscopy imaging equipment, neither relocating existing manufacturing facilities to the United States nor establishing new domestic facilities would be commercially viable.

Without overseas manufacturing, these Inventions would likely not be commercialized. Thus, the enhanced capabilities that these Inventions can provide to fluorescence microscopy would likely not be available for most researchers. Waiver of the domestic manufacturing preference would allow enhanced super-resolution fluorescence microscopy equipment to enter the market.

Respectfully submitted,

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Pages 17 through 526 redacted for the following reasons:
- -
Patent documents - not requested
PubMed
Nat Methods. Author manuscript; available in PMC 2009 June 23.
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Nat Methods. 2006 October; 3(10): 793–795.
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